Diastolic Carotid Artery Wall Shear Stress Is Associated With Cerebral Infarcts and Periventricular White Matter Lesions

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Background and Purpose—Low wall shear stress (WSS) is an early marker in the development of vascular lesions. The present study aims to assess the relationship between diastolic and systolic WSS in the internal carotid artery and periventricular (PWML), deep white matter lesions, and cerebral infarcts (CI).

Methods—Early, mid, and late diastolic and peak systolic WSS were derived from shear rate obtained by gradient echo phase contrast magnetic resonance sequences multiplied by individually modeled viscosity. PWML, deep white matter lesions, and CI were derived from proton density (PD), T2, and fluid attenuated inversion recovery (FLAIR) MRI in 329 participants (70–82 years; PROSPER baseline). Analyses were adjusted, if appropriate, for age, gender, intracranial volume, and multiple cardiovascular risk factors.

Results—Mid-diastolic WSS was significantly correlated with the presence of PWML (B = −10.15; P = 0.006) and CI (B = −2.06; P = 0.044), but not with deep white matter lesions (B = −1.30; P = 0.050; adjusted for age, gender, WML, and intracranial volume). After adjustment for cardiovascular risk factors, these correlations weakened but remained significant. Systolic WSS was not correlated with any of the cerebrovascular parameters.

Conclusions—This study is the first to our knowledge to present a cross-sectional correlation between carotid artery WSS and cerebrovascular pathology such as PWML and CI in a large population. Furthermore, it shows that diastolic hemodynamics may be more important than systolic or mean hemodynamics. Future studies exploring vascular hemodynamic damage should focus on diastolic WSS.

Key Words: carotid artery • cerebral infarct • hemodynamics • wall shear stress • white matter lesions
The present study aims to evaluate whether WSS in the internal carotid artery is associated with white matter lesions (WML) and cerebral infarcts (CI), 2 neuroradiological markers that are frequently found on cranial MRI. In addition to mean WSS, we analyzed diastolic and systolic WSS separately.

Materials and Methods

Participants

Data for this study were drawn from the baseline of the Dutch MRI substudy of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). This randomized controlled trial examines the effect of pravastatin on cardiovascular and cerebrovascular events in elderly individuals, aged 70 to 82 years, with vascular disease or at high vascular risk. The inclusion and exclusion criteria of PROSPER were described in the PROSPER study setup. At baseline, 329 of the PROSPER participants underwent MRI of both internal carotid arteries 3 cm cranial to the carotid bifurcation. All participants refrained from smoking for at least 90 minutes before the examination. Measurements from both internal carotid arteries were averaged.

Wall Shear Stress Computation

WSS is defined as viscosity multiplied by shear rate (ie, the gradient of blood velocity with respect to the vessel wall). Shear rate values were extracted from flow measurements fit on the previously described 3-dimensional paraboloid method, within semiautomatically delineated vessels, using the in-house developed software package FLOW (Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands). Viscosity and its shear-thinning properties (ie, the decrease of viscosity after an increase of shear rate) were modeled by the Carreau-Yasuda model. Values from the well-tested blood-mimicking KSCN-X solution were individually adjusted for hematocrit with the following equation:

\[
V_{\text{iscosity}} = 2.2 + (22 - 2.2) \times (1 + 0.11 \times \text{shear rate}^{0.644})^{\text{hematocrit} - 10.644}
\]

Individual hematocrit values were obtained from 4 mL blood withdrawn from the antecubital vein of sober participants and collected in a 7.2-mg K$_2$EDTA sterile collecting tube using a Sysmex XE-2100 Automated Hematology Analyzer (TOA Medical Electronics).

Cerebral Pathology

Quantification of WML volumes was performed by in-house developed automated lesion detection software. For postprocessing, PD, FLAIR, and T2-weighted MRI were transferred to an offline workstation. By combining fuzzy clustering, connectivity rules, and mathematical morphology, WML segmentations were generated automatically. WML were defined as regions being hyperintense on both proton density-weighted MRI and T2-weighted MRI. Lesions were divided into periventricular WML (PWML) and deep WML (DWML) based on their connection to the lateral ventricles. To correct for incidental inclusion of cerebrospinal fluid and gray matter, the automatically generated WMH segmentations were edited manually by a trained rater with >20 years of neuroradiological experience (M.A.v.B.). FLAIR scans were used as a reference to rule out other pathogenesis or the entanglement of WMH with Virchow-Robin spaces. Infratentorial lesions (brain stem and cerebellum) were excluded.

Infarcts were identified by an experienced neuroradiologist (M.A.v.B.) with >20 years of neuroradiological experience and defined as a parenchymal defect: (1) having the same signal intensity as cerebrospinal fluid on all pulse sequences; (2) surrounded by a tissue rim with increased signal intensity on PD, T2, and FLAIR; (3) with a vascular distribution; and (4) without a mass effect. Hemorrhagic infarcts were excluded based on the presence of hemosiderin in the wall of the parenchymal defect on the susceptibility-weighted scan. All measurements were performed blinded to participant identity, age, and gender.

Statistical Analysis

All statistical analyses were performed with the statistical software package SPSS for Windows, release 17.0 (SPSS). Relations between gender and age and WSS and the cerebrovascular parameters were investigated by linear regression analysis. Relations between the WSS clusters and cerebrovascular pathology parameters were investigated by 2 linear regression models. Model 1 only adjusted for age, gender, and total intracranial volume, and model 2 additionally adjusted for the cardiovascular risk factors of alcohol use, systolic and diastolic blood pressure, low-density lipoprotein, high-density lipoprotein, total and total/high-density lipoprotein cholesterol, triglycerides, history of vascular disease, history of hypertension or history of diabetes mellitus, and glucose. The exact measurement methods of these parameters are previously described in the PROSPER study setup.
The level of significance was set at $P<0.05$. No violations of the usual regression assumptions were detected.

## Results

Of the enrolled participants, 184 (56%) were men. Age ranged from 70 to 82 years, with a median of 74 years, with 25% and 75% interquartile ranges of 72 and 77 years. These and other characteristics are shown in Table 1. Men had PWML and DWML volume (mL) 4.15 ± 8.84 and 1.00 ± 1.56 (B = -0.025, $P<0.05$). After adjustment for cardiovascular risk factors, PWML and DWML were associated with CI (Table 4). Mean WSS was correlated with total WML volume (B = -7.39; $P<0.05$), PWML (B = -7.02; $P<0.05$), and CI (B = -1.53; $P<0.05$), but not with DWML (B = -0.77; $P=0.165$; Tables 2 and 3). All WSS clusters were significantly and inversely correlated with PWML, but none was correlated with DWML. The strongest correlation with PWML was shown in mid-diastole (B = -10.15; $P=0.006$) and the weakest was shown in peak systole (B = -4.03; $P=0.044$). After adjustment for cardiovascular risk factors, only peak systolic WSS lost its significance. The highest correlation with DWML was found in mid-diastole, which was borderline significant (B = -1.30; $P=0.050$). All WSS clusters except for peak systolic WSS were associated with CI (Table 4). Mid-diastolic WSS showed the highest correlation (B = -2.06; $P=0.015$), where peak systolic WSS showed the weakest correlation (B = -0.79; $P=0.089$). After adjustment for cardiovascular risk factors, this correlation of both mean and early diastolic WSS lost significance.

## Discussion

The most important findings of this study are that WSS in the internal carotid artery is inversely correlated with PWML and CI, but not with DWML. Overall, diastolic WSS showed more significant correlations than systolic WSS.

The association between carotid and cerebrovascular pathology has been elaborately studied.4,5 However, only a limited number of studies investigated the influence of WSS on cerebrovascular pathology. One study reported an association between unilateral ischemic stroke and lower mean WSS in the ipsilateral common carotid artery.16 Likewise, low internal carotid and basilar artery WSS have been related to mild cognitive impairment and Alzheimer disease.17 Intracranially, both lower and higher intracranial WSS were correlated with intracranial stenoses and aneurysm growth and rupture.18 Apart from associations with focal and distal vascular damage, WSS was previously associated with a variety of systemic vascular risk factors.1,3–7 The associations described in this study could have their origin in a direct effect that carotid artery hemodynamics have on the incidence of cerebrovascular pathology, such as artery-to-artery microemboli. Still, a relationship of disrupted cerebrovascular hemodynamics that develops in an equal trend when

### Table 1. Characteristics of Study Participants (n=329)

<table>
<thead>
<tr>
<th>Findings</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (25%, 75% interquartile ranges in y)</td>
<td>74 (72–77)</td>
</tr>
<tr>
<td>Men</td>
<td>184 (56%)</td>
</tr>
<tr>
<td>PWML volume (mL)</td>
<td>4.15 ± 8.84</td>
</tr>
<tr>
<td>DWML volume (mL)</td>
<td>1.00 ± 1.56</td>
</tr>
<tr>
<td>CI (n)</td>
<td>1.05 ± 1.95</td>
</tr>
<tr>
<td>Total count of CI</td>
<td>324</td>
</tr>
<tr>
<td>Intracranial volume (mL)</td>
<td>1399 ± 148</td>
</tr>
</tbody>
</table>

CI indicates cerebral infarct; DWML, deep white matter lesion; PWML, periventricular white matter lesion.

Of continuous variables, the mean ± SD are shown. For the categorical variable gender, findings are presented in count of men with percentages shown in parentheses.

### Table 2. Cross-Sectional Associations of Early, Mid, and Late Diastolic and Peak Systolic Wall Shear Stress With Periventricular White Matter Lesions

<table>
<thead>
<tr>
<th>Periventricular White Matter Lesion</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>CI</td>
<td>$P$</td>
</tr>
<tr>
<td>Mean WSS (Pa)</td>
<td>-7.02</td>
<td>-13.15× -0.90</td>
</tr>
<tr>
<td>Early diastolic WSS (Pa)</td>
<td>-7.39</td>
<td>-13.90× -0.89</td>
</tr>
<tr>
<td>Mid-diastolic WSS (Pa)</td>
<td>-10.15</td>
<td>-17.41× -2.89</td>
</tr>
<tr>
<td>Late diastolic WSS (Pa)</td>
<td>-8.63</td>
<td>-16.27× -1.00</td>
</tr>
<tr>
<td>Peak systolic WSS (Pa)</td>
<td>-4.03</td>
<td>-7.94× -0.11</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>CI</td>
</tr>
<tr>
<td>Mean WSS (Pa)</td>
<td>-6.76</td>
<td>-13.04× -0.47</td>
</tr>
<tr>
<td>Early diastolic WSS (Pa)</td>
<td>-7.09</td>
<td>-13.85× -0.32</td>
</tr>
<tr>
<td>Mid-diastolic WSS (Pa)</td>
<td>-9.36</td>
<td>-16.85× -1.86</td>
</tr>
<tr>
<td>Late diastolic WSS (Pa)</td>
<td>-8.55</td>
<td>-16.44× -0.66</td>
</tr>
<tr>
<td>Peak systolic WSS (Pa)</td>
<td>-3.96</td>
<td>-8.07× -0.17</td>
</tr>
</tbody>
</table>

Associations were assessed by linear regression models. Model 1 adjusted for age, gender, and total intracranial volume. Model 2 also adjusted for cardiovascular risk factors.

Each estimate presents the cross-sectional association of WSS with white matter lesions. WSS represents carotid artery wall shear stress. B is a regression coefficient. CI represents lower and upper 95% confidence intervals of B.

CI indicates confidence interval; WSS, wall shear stress.

* $P<0.05$.
† $P<0.01$. 

P<0.01.
Table 3: Cross-Sectional Associations of Early, Mid, and Late Diastolic and Peak Systolic Wall Shear Stress With Deep White Matter Lesions

<table>
<thead>
<tr>
<th></th>
<th>Mean WSS (Pa)</th>
<th>Early diastolic WSS (Pa)</th>
<th>Mid-diastolic WSS (Pa)</th>
<th>Late diastolic WSS (Pa)</th>
<th>Peak systolic WSS (Pa)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>CI</td>
<td>P</td>
<td>B</td>
<td>CI</td>
</tr>
<tr>
<td>Model 1</td>
<td>-0.77</td>
<td>-1.85 × 0.32</td>
<td>0.165</td>
<td>-0.92</td>
<td>-2.08 × 0.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.20 × 0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.087</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-3.07</td>
<td>-1.07 × 0.33</td>
<td>0.301</td>
<td>-0.40</td>
<td>-1.13 × 0.33</td>
</tr>
</tbody>
</table>

Associations were assessed by linear regression models. Model 1 adjusted for age, gender, and total intracranial volume. Model 2 also adjusted for cardiovascular risk factors.

CI indicates confidence interval; WSS, wall shear stress.

Exposed to identical systemic risk factors cannot be excluded. Moreover, any causal correlation between carotid hemodynamics and cerebrovascular pathology could be confounded by similar worsening hemodynamics in the cardiac, vertebrobasilar, or cerebral arteries.20

In this study PWML, but not DWML, were associated with WSS. Interestingly, previous investigators have found a similar distinction as PWML, but not DWML, were associated with total cerebral blood flow, intima-media thickness, plaques in the carotid artery, and atrial fibrillation.15,21,22 An explanation may be found in their suspected dissimilar etiology. PWML are large, diffuse, and symmetrical, suggesting global vascular damage. DWML, however, are typically small and asymmetrical, which suggests focal perfusion disturbances.21,22 The association of carotid artery WSS with PWML may be mainly explained from a systemical relationship of carotid and cerebrovascular hemodynamics worsening in an equal trend.

CI are typically linked to a direct relationship, and carotid artery WSS may predict atherosclerotic pathology that directly leads to thromboembolic processes responsible for CI.1,4,8,23 Cross-sectional associations of WSS with CI have not, to our knowledge, been demonstrated before. Still, 1 study reported a lower mean WSS in the common carotid artery ipsilateral to unilateral ischemic stroke, accompanied by more evident atherosclerotic plaques at the same side.16 A major strength of this study is its individually modeled viscosity values as opposed to a fixed value used by other studies.14 Another major strength of the methods used in this study are the 4-dimensional (3-dimensional + time) MR measurements of WSS requiring minimal manual intervention.12 The dynamics of WSS in 1 cardiac cycle are illustrated in the Figure. Unfortunately, whereas MR has a high spatial resolution for WSS computations, it has a low temporal resolution compared to duplex ultrasonography. Moreover, by retrospectively averaging the heart rate, temporal variations in and between individuals, such as differences in vessel lengths and vessel compliances, are not taken into account. As a consequence, distinct WSS values of cardiac phases fade as they mix with neighboring phases. This disadvantage may especially burden systolic WSS because it experiences the fastest dynamic shear stress changes. Interestingly, mid-diastolic WSS experiences the slowest dynamic changes in WSS and showed the highest correlations. This may partly explain the absence of correlations found in systole as compared to diastole. Likewise, other studies have found most or best correlations with diastolic WSS.6,17,24 Maybe diastolic WSS is a more sensitive parameter for detecting vascular pathol-

Table 4: Cross-Sectional Associations of Early, Mid, and Late Diastolic and Peak Systolic Wall Shear Stress With Confidence Intervals

<table>
<thead>
<tr>
<th></th>
<th>CI (n) Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>CI</td>
</tr>
<tr>
<td>Mean WSS (Pa)</td>
<td>-1.53</td>
<td>-2.92 × -0.14</td>
</tr>
<tr>
<td>Early diastolic WSS (Pa)</td>
<td>-1.50</td>
<td>-2.99 × -0.02</td>
</tr>
<tr>
<td>Mid-diastolic WSS (Pa)</td>
<td>-2.06</td>
<td>-3.72 × -0.40</td>
</tr>
<tr>
<td>Late diastolic WSS (Pa)</td>
<td>-2.00</td>
<td>-3.74 × -0.25</td>
</tr>
<tr>
<td>Peak systolic WSS (Pa)</td>
<td>-0.79</td>
<td>-1.69 × -0.12</td>
</tr>
</tbody>
</table>

Associations were assessed by linear regression models. Model 1 adjusted for age, gender, and total intracranial volume. Model 2 also adjusted for cardiovascular risk factors.

CI indicates confidence interval; WSS, wall shear stress.

*P<0.05.
ogy. Another possible explanation, previously hypothesized by Irace et al., is a WSS threshold value. We also hypothesized the existence of a threshold level of WSS, below which vascular pathology only occurs. This would explain why a decrease of peak systolic WSS does not, but diastolic WSS does, increase vulnerability.

Conclusions
This study is the first to our knowledge to present a cross-sectional correlation between carotid artery WSS and cerebrovascular pathology such as periventricular WML and CI in a large population. It shows that diastolic hemodynamics may be more important than systolic or mean hemodynamics. Disturbed WSS may present early atherogenesis and may predict possible damage in an earlier stage than current markers for large vessel disease. The results of the present study should encourage new longitudinal WSS studies to test the clinical predictive value of WSS measurements in relation to current standards.

Appendix
In the present study, only subjects were included who were participants from the nested MRI substudy of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). The PROSPER Study Group consists of: (Glasgow) J. Shephard (chairman and principal investigator), S.M. Cobbe, I. Ford, A. Gaw, P.W. Macfarlane, C.J. Packard, and D.J. Stott; (Leiden) G.J. Blauw (principal investigator), E.L.E.M. Bol len, A.M. Kamper, and R.G.J. Westendorp; (Cork) M.B. Murphy (principal investigator), B.M. Buckely, M. Hyland, and I.J. Perry.

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Disclosures
None.

References

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